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Review

Mechanisms of humoral immune response against *Pseudomonas aeruginosa* biofilm infection in cystic fibrosis

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Abstract

P. aeruginosa chronic lung infection is the major cause of morbidity and mortality in patients with cystic fibrosis (CF), and is characterized by a biofilm mode of growth, increased levels of specific IgG antibodies and immune complex formation. However, despite being designed to combat this infection, such elevated humoral response is not associated with clinical improvement, pointing to a lack of anti-pseudomonas effectiveness. The mode of action of specific antibodies, as well as their structural features, and even the background involving B-cell production, stimulation and differentiation into antibody-producing cells in the CF airways are poorly understood. Thus, the aim of this review is to discuss studies that have addressed the intrinsic features of the humoral immune response and provide new insights regarding its insufficiency in the CF context.

Keywords: Cystic fibrosis; *Pseudomonas aeruginosa*; Lung infection; Humoral immune response; Antibodies

Contents

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1. Introduction

Pulmonary disease is the preponderant manifestation in cystic fibrosis (CF), where a dehydration in the airway surface liquid (ASL) leads to mucus accumulation in the lower airways, impairing the mucociliary clearance (MCC) and facilitating colonization and infection of the lower airway environment by bacterial pathogens, especially *Pseudomonas aeruginosa*, the major morbidity and mortality cause in the CF population [1]. *P. aeruginosa* infection starts with a non-mucoid planktonic variant, which is frequently succeeded by colonization-treatment-recolonization cycles, marked by intermittent bacterial isolations in microbiological respiratory tract cultures. This can further develop into a chronic stage of infection, marked by a mucoid biofilm-growing *P. aeruginosa*. Biofilm formation provides protection against the immune system (Figs. 1 and 2) and antibiotics, as well as provoking an intense inoperative tissue-damaging inflammatory response, rendering *P. aeruginosa* practically impossible to eradicate in this phase of infection [2,3]. Moreover, the ionic unbalance caused by the CFTR defects leads to changing chemical characteristics of the ASL, where an acidified environment is formed, reducing or inactivating defensins, lysozymes and lactoferrins, natural defense molecules of the primary airway barrier, making bacterial killing even more difficult [4,5].

Still, a number of studies in the last two decades have shown that not only the primary immune barriers are impaired in the CF airways, but also the cellular and signaling artifacts of the immune system as a whole is involved [6]. An interesting fact is that such impairment does not necessarily mean deficiency, but mostly overproduction of several immune components. CF airway epithelial cells (AECs), when challenged with *P. aeruginosa*, show increased activation of the Nuclear Transcription Factor – Kappa B (NF-κB), which leads to overproduction of pro-inflammatory cytokines interleukin (IL-) 6 and 8, and Tumor Necrosis Factor Alpha (TNF-α) disproportionately to the bacterial load in the airways, when compared with normal AECs. NF-κB overproduction also reduces the synthesis of glutathione, an antioxidant peptide that neutralizes reactive oxygen species (ROS) and increases the production of inflammatory mediators like

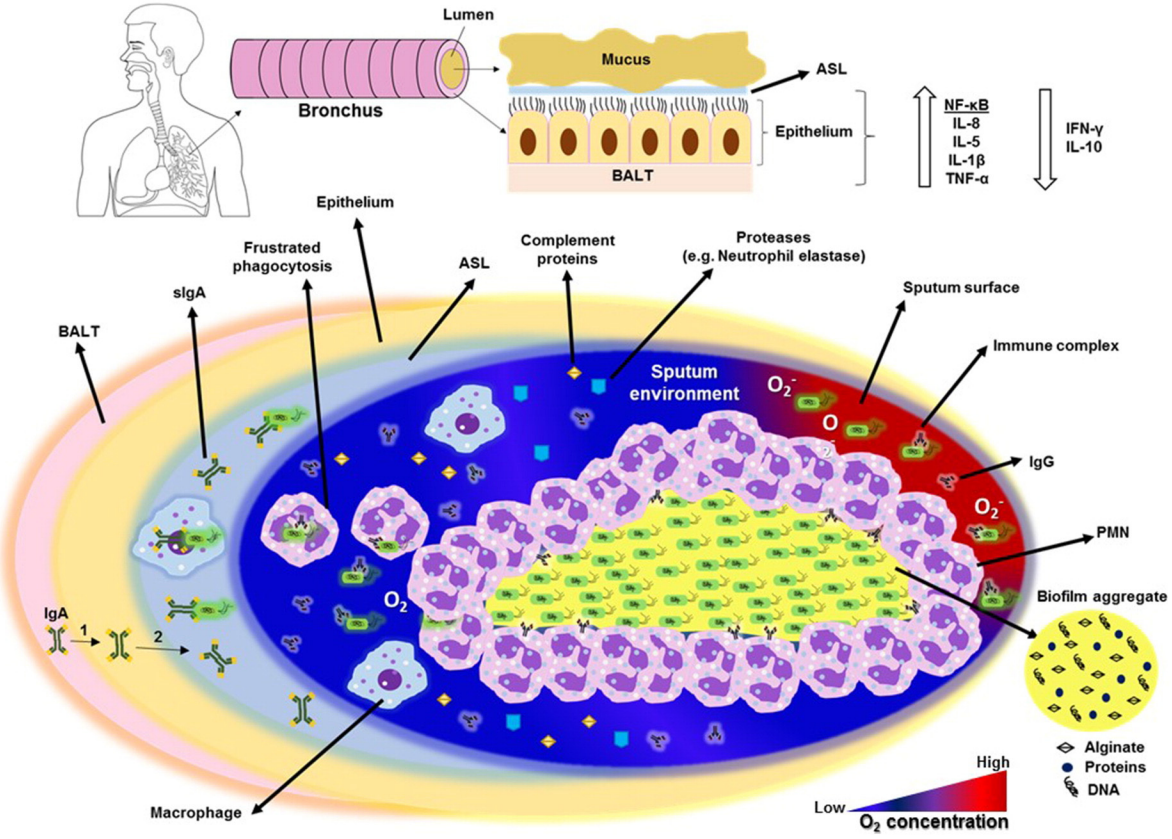

Fig. 1. Mucus with a *P. aeruginosa* biofilm surrounded by polymorphonuclear neutrophils (PMN) and IgG antibodies specific to *P. aeruginosa* antigens, such as alginate, LPS and proteins. Immune complexes are formed between *P. aeruginosa* antigens and IgG, which activate complement and attract PMNs. Activated PMNs consume oxygen and liberate ROS, proteases and DNA, starting the inflammatory reaction. Such inflammatory reaction consumes all oxygen in mucus, which becomes anaerobic, impairing the PMNs' ability to phagocytose and kill *P. aeruginosa* in sputum due to the oxygen starvation needed for PMN activity, and leading to a frustrated phagocytosis. The pronounced IgG antibody response occurs especially due to the high NF-κB production by CF airway epithelial cells (AECs), and to the Th2-skewing of the adaptive immune reponse, resulting in hyperproduction of proinflammatory cytokines, like IL-5 and IL-8, and low production of anti-inflammatory cytokines, like IL-10 and INF-γ. Since the PMNs' ability is impaired, this hyperinflammatory response leads to tissue damage rather than killing *P. aeruginosa* biofilms. IgA is produced in the Bronchi-Associated Lymphoyd Tissue (BALT) submucosa (**1**), where it combines with the secretory component, yielding sIgA, which is exported through the epithelial cells to the airway surface liquid (ASL) (**2**), preventing *P. aeruginosa* to attach to the epithelial cells, in a macrophage-mediated non-phlogistic response, thereby not contributing to airway inflammation.

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